

**SCREENING-LEVEL HAZARD CHARACTERIZATION
OF HIGH PRODUCTION VOLUME CHEMICALS**

SPONSORED CHEMICAL

**Cashew Nutshell Liquid (CAS No. 8007-24-7)
[9th CI Name: Cashew, nutshell liq.]**

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INTERIM**

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SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

The High Production Volume (HPV) Challenge Program¹ is a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsor chemicals; sponsorship entails the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data do not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to “SIDS” (Screening Information Data Set^{1,2}) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency’s Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1,400 sponsored chemicals. OPPT is using a hazard-based screening process to prioritize review of the submissions. The hazard-based screening process consists of two tiers described below briefly and in more detail on the Hazard Characterization website³.

Tier 1 is a computerized sorting process whereby key elements of a submitted data set are compared to established criteria to “bin” chemicals/categories for OPPT review. This is an automated process performed on the data as submitted by the sponsor. It does not include evaluation of the quality or completeness of the data.

In Tier 2, a screening-level hazard characterization is developed by EPA that consists of an objective evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. The evaluation is performed according to established EPA guidance^{2,4} and is based primarily on hazard data provided by sponsors. EPA may also include additional or updated hazard information of which EPA, sponsors or other parties have become aware. The hazard characterization may also identify data gaps that will become the basis for a subsequent data needs assessment where deemed necessary. Under the HPV Challenge Program, chemicals that have similar chemical structures, properties and biological activities may be grouped together and their data shared across the resulting category. This approach often significantly reduces the need for conducting tests for all endpoints for all category members. As part of Tier 2, evaluation of chemical category rationale and composition and data extrapolation(s) among category members is performed in accord with established EPA² and OECD⁵ guidance.

The screening-level hazard characterizations that emerge from Tier 2 are important contributors to OPPT’s existing chemicals review process. These hazard characterizations are technical documents intended to support subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public. The public, including sponsors, may offer comments on the hazard characterization documents.

The screening-level hazard characterizations, as the name indicates, do not evaluate the potential risks of a chemical or a chemical category, but will serve as a starting point for such reviews. In 2007, EPA received data on uses of and exposures to high-volume TSCA existing chemicals, submitted in accordance with the requirements of the Inventory Update Reporting (IUR) rule. For the chemicals in the HPV Challenge Program, EPA will review the IUR data to evaluate exposure potential. The resulting exposure information will then be combined with the screening-level hazard characterizations to develop screening-level risk characterizations^{4,6}. The screening-level risk characterizations will inform EPA on the need for further work on individual chemicals or categories. Efforts are currently underway to consider how best to utilize these screening-level risk characterizations as part of a risk-based decision-making process on HPV chemicals which applies the results of the successful U.S. High Production Volume Challenge Program and the IUR to support judgments concerning the need, if any, for further action.

¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

² U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

³ U.S. EPA. HPV Chemicals Hazard Characterization website (<http://www.epa.gov/hpvis/abouthc.html>).

⁴ U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

⁵ OECD. Guidance on the Development and Use of Chemical Categories; <http://www.oecd.org/dataoecd/60/47/1947509.pdf>.

⁶ U.S. EPA. Risk Characterization Program; <http://www.epa.gov/osa/spc/2riskchr.htm>.

SCREENING-LEVEL HAZARD CHARACTERIZATION Cashew Nutshell Liquid (CAS No. 8007-24-7)

Introduction

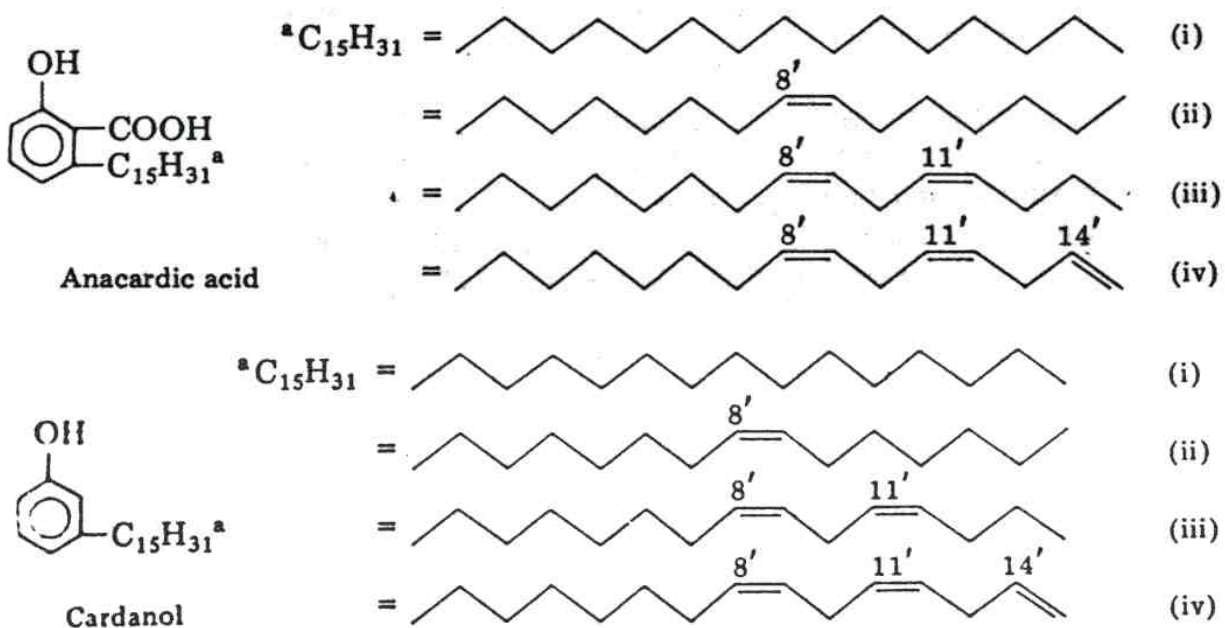
The sponsor, Cardolite Corporation, submitted a Test Plan and Robust Summaries to EPA for Cashew Nutshell Liquid (CAS No. 8007-24-7; 9th CI Name: Cashew Nutshell Liq.) on June 5, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on June 5, 2002

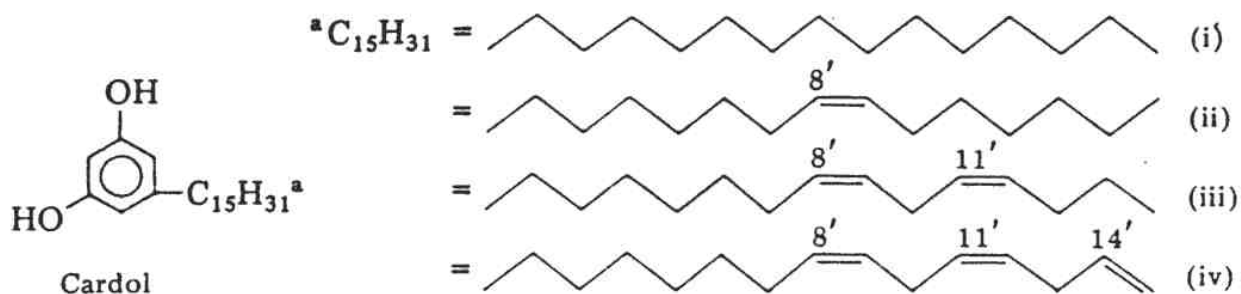
(<http://www.epa.gov/chemrtk/pubs/summaries/casntliq/c13793tc.htm>). EPA comments on the original submission were posted to the website on November 12, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on December 20, 2002, November 2, 2006 and April 6, 2007, which were posted to the ChemRTK website on January 21, 2003, November 16, 2006 and July 24, 2007, respectively.

This screening-level hazard characterization is based primarily on the review of the test plan and robust summaries of studies submitted by the sponsor(s) under the HPV Challenge Program. In preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. A summary table of SIDS endpoint data with the structure(s) of the sponsored chemical(s) is included in the appendix. The screening-level hazard characterization for environmental and human health toxicity is based largely on SIDS endpoints and is described according to established EPA or OECD effect level definitions and hazard assessment practices.

Cashew nut shell liquid (CNSL) is obtained from the shell of a cashew nut and is one of the sources of naturally occurring phenols. About 30-35% CNSL is present in the shell, which amounts to approximately 67% of the nut. CNSL is traditionally obtained as a by-product during the process of removing the cashew kernel from the nut. Natural (i.e. cold, solvent extracted) CNSL is a liquid that contains approximately 70% anacardic acid, 18% cardol, and 5% cardanol (Fig 1), with the remainder being made up of other phenols and less polar substances. Anacardic acid, cardanol and cardol consist of mixtures of components having various degrees of unsaturation in the alkyl side-chain.

Figure 1: Structures of Anacardic acid, Cardanol and Cardol





In technical (i.e. heat extracted) CNSL, the heating process leads to decarboxylation of the anacardic acid to form cardanol. Typically, the composition of technical CNSL is approximately 52% cardanol, 10% cardol, 30% polymeric material, with the remainder being made up of other substances. The technical CNSL is often further processed by distillation at reduced pressure to remove the polymeric material. The composition of distilled technical CNSL (Cardolite NC 511) is approximately 78% cardanol, 8% cardol, 2% polymeric material, < 1% 2-methyl cardanol, 2.3% heptadecyl homologue triene, 3.8% heptadecyl homologue diene and the remainder other homologous phenols.

Summary-Conclusion

The log K_{ow} of cashew nutshell liquid indicates its potential to bioaccumulate is expected to be high. Cashew nutshell liquid is readily biodegradable, indicating that it is not expected to persist in the environment.

The sponsor did not submit measured aquatic toxicity data for cashew nutshell liquid, but provided acute toxicity values estimated by ECOSAR for cardanol and cardol, the two major components of cashew nutshell liquid. The toxicity data estimated by ECOSAR for fish, aquatic invertebrates and aquatic plants indicates the potential acute hazard of cashew nutshell liquid is high.

Acute oral toxicity of cashew nutshell liquid in rats is low. Cashew nutshell liquid is a strong dermal sensitizer. Following repeated oral exposure of rats to cashew nutshell liquid in a combined repeated-dose/reproductive/developmental screening test, the target organs for toxicity were the liver, lungs, stomach and mesenteric lymph node. Slightly reduced body weight, increased salivation, hematological and clinical biochemistry effects were also noted. Females had increased relative liver weights. Histopathological changes in the organs at the high-dose included higher incidence of alveolar macrophages in the lungs in females, sinus histiocytosis and/or foamy histiocytes in the mesenteric lymph nodes, hyperkeratosis and acanthosis of the forestomach in both sexes and duodenum-mucosal hypertrophy in males. No effects on reproductive or developmental parameters were noted in the study. Cashew nutshell liquid did not induce gene mutations and chromosomal aberrations.

The potential health hazard of cashew nutshell liquid is low.

No data gaps were identified under the HPV Challenge Program.

1. Physical-Chemical Properties and Environmental Fate

A summary of physical-chemical properties and environmental fate data submitted is provided in Appendix. For the purpose of the screening-level hazard characterization, the review and summary of these data was limited to the octanol-water partition coefficient and biodegradation endpoints as indicators of bioaccumulation and persistence, respectively.

Octanol-Water Partition Coefficient

Log K_{ow} : > 6.2

Biodegradation

In a closed bottle ready biodegradation test using fresh activated sludge from a municipal biological sewage treatment plant as inoculum, 96% of Cardolite NC 511 (distilled cashew nut shell liquid) had degraded after 28 days. **Cashew nutshell liquid is readily biodegradable.**

Conclusion: The log K_{ow} of cashew nutshell liquid indicates its potential to bioaccumulate is expected to be high. Cashew nutshell liquid is readily biodegradable, indicating that it is not expected to persist in the environment.

2. Environmental Effects – Aquatic Toxicity

The sponsor did not submit measured aquatic toxicity data for cashew nutshell liquid, but provided acute toxicity values estimated by ECOSAR for cardanol and cardol, the two major components of cashew nutshell liquid. In comments on the original test plan, EPA stated that ECOSAR estimates were not adequate to address aquatic toxicity endpoints suggested that a chronic fish toxicity test be performed. These comments were based on projections of very high log K_{ow} (> 8.0) and very low solubility of cashew nutshell liquid and/or its components. As part of the HPV Challenge program, the sponsor submitted measured data for log K_{ow} and water solubility. EPA's review of these data indicate that the log K_{ow} is lower than anticipated (> 6.2) and water solubility is greater than anticipated (0.305 mg/L). Furthermore, the ready biodegradation data (96% in 28 days and > 60% within 10-day window) suggest that it is less unlikely that chronic exposures to aquatic organisms will occur in the environment. Therefore, EPA has not identified chronic fish toxicity testing as a data gap.

Acute Toxicity to Fish

Cardanol (CAS No. 37330-39-5, Component chemical)

A 96-hour LC_{50} for fish estimated by ECOSAR for the component chemical, cardanol, was provided to support evaluation of the acute toxicity of cashew nutshell liquid.

96-h LC_{50} = 0.002 – 0.005 mg/L

Cardol (CAS No. 57486-25-6, Component chemical)

A 96-hour LC_{50} for fish estimated by ECOSAR for the component chemical, cardol, was provided to support evaluation of the acute toxicity of cashew nutshell liquid.

96-h LC_{50} = 0.005 – 0.011 mg/L

Acute Toxicity to Aquatic Invertebrates

Cardanol (CAS No. 37330-39-5, Component chemical)

A 48-hour LC_{50} for daphnia estimated by ECOSAR for the component chemical, cardanol, was provided to support evaluation of the acute toxicity of cashew nutshell liquid.

48-h EC_{50} = 0.024 – 0.040 mg/L

Cardol (CAS No. 57486-25-6, Component chemical)

A 48-hour LC₅₀ for daphnia estimated by ECOSAR for the component chemical, cardol, was provided to support evaluation of the acute toxicity of cashew nutshell liquid.

48-h EC₅₀ = 0.039 – 0.066 mg/L

Toxicity to Aquatic Plants

Cardanol (CAS No. 37330-39-5, Component chemical)

A 96-hour LC₅₀ for algae estimated by ECOSAR for the component chemical, cardanol, was provided to support evaluation of the acute toxicity of cashew nutshell liquid.

96-h LC₅₀ = 0.00011 – 0.00034 mg/L

Cardol (CAS No. 57486-25-6, Component chemical)

A 96-hour LC₅₀ for algae estimated by ECOSAR for the component chemical, cardol, was provided to support evaluation of the acute toxicity of cashew nutshell liquid.

96-h LC₅₀ = 0.00031 – 0.00096 mg/L

Conclusion: The sponsor did not submit measured aquatic toxicity data for cashew nutshell liquid, but provided acute toxicity values estimated by ECOSAR for cardanol and cardol, the two major components of cashew nutshell liquid. The toxicity data estimated by ECOSAR for fish, aquatic invertebrates and aquatic plants indicates the potential acute hazard of cashew nutshell liquid is high.

3. Human Health Effects

Acute Oral Toxicity

Acute toxicity data conducted according to established guidelines were not submitted. However, during a range-finding study for the repeated-dose toxicity study with reproductive/developmental toxicity screening test (see below), Sprague-Dawley rats (3/sex/dose) were orally dosed with 0 or 1,000 mg/kg-bw/day for 14 days. No mortality occurred during the 14 day treatment period. No clinically observable signs of toxicity were observed. A slight reduction in body weight gain was observed for animals treated with the test substance compared to controls. No macroscopic abnormalities were observed at necropsy.

LD₅₀ > 1000 mg/kg-bw

Repeated-Dose Toxicity

In a combined repeated-dose/reproductive/developmental toxicity screening test, groups of Sprague-Dawley rats (10 sex/dose) were dosed via gavage daily at 0, 15, 150, or 1000 mg/kg-bw/day for up to 49 days. Slightly reduced body weight was observed in high-dose males during the first two weeks of the study and in females during the later stages of gestation. Increased salivation was noted in animals of both sexes at the high-dose level after day 9. High-dose females had increased relative liver weights. Hematological changes (elevated platelet, hemoglobin, erythrocyte, and hematocrit counts, elevated mean cell volume, and decreased mean cell hemoglobin concentration) were noted in high-dose males. An increase in mean cell volume was also noted in high-dose females. Clinical biochemistry changes (elevated aspartate and alanine aminotransferases, alkaline phosphatase, and inorganic phosphorus, reduction in cholesterol and elevated bilirubin) were noted in males and females at the high dose. High-dose males also had increased plasma urea, reduced glucose levels, and elevated albumin/globulin ratios. Histopathological changes at the high dose included higher incidence of alveolar macrophages in the lungs in females, sinus histiocytosis and/or foamy histiocytes in the mesenteric lymph nodes, hyperkeratosis and acanthosis of the forestomach in both sexes and duodenum-mucosal hypertrophy in males.

LOAEL = 1000 mg/kg-bw/day (based on effects to the liver, lungs, stomach, mesenteric lymph nodes, hematology and clinical biochemistry)

NOAEL = 150 mg/kg-bw/day

Reproductive/Developmental Toxicity

In the combined repeated-dose/reproductive/developmental toxicity screening test described previously, no adverse effects were detected on mating performance, fertility, precoital interval, duration of gestation, gestation index, number of implantations, or number of corpora lutea. No treatment related changes were noted in litter size, weight, sex ratio, viability index, post-natal growth rate or toxicologically significant effects on offspring. Systemic effects on the parental generation are described in the repeated-dose toxicity section above.

LOAEL (systemic toxicity) = 1000 mg/kg-bw/day (based on effects described in the repeated-dose section above)

NOAEL (systemic toxicity) = 150 mg/kg-bw/day

LOAEL (reproductive/developmental toxicity) > 1000 mg/kg-bw/day

NOAEL (reproductive/developmental toxicity) = 1000 mg/kg-bw/day (based on no effects at the highest dose tested)

Genetic Toxicity – Gene Mutation

In vitro

(1) *Salmonella typhimurium* strains (TA98, TA100, TA1535, TA1537 and TA1538) were exposed to cashew nutshell liquid at concentrations of 50, 150, 500, 1500 or 5000 µg/plate in the presence and absence of metabolic activation. The cytotoxic concentration was greater than 5000 µg/plate. A precipitate was observed at 1500 and 5000 µg/plate but it did not impact the scoring of colonies. No significant increase in the frequency of revertant colonies was recorded for any of the bacterial strains at any concentration, either with or without metabolic activation. Positive and solvent controls were tested and responded appropriately.

Cashew nutshell liquid was not mutagenic in this assay.

(2) Chinese Hamster Ovary (CHO-KI BH4) cells were exposed to cashew nutshell liquid, in two experiments, in the presence and absence of metabolic activation. In experiment 1 the concentrations ranged from 0.75 – 18 µg/mL and in the second experiment, the concentration range was 0.75 – 24 µg/mL. Two replicates were conducted per experiment. Positive and solvent controls were tested and responded appropriately. The cytotoxic concentration with and without metabolic activation was 47.19 µg/mL (in the text, though the tables stated 24 µg/mL was toxic with activation). The test substance did not induce significant or dose-related mutant frequency in the presence or absence of metabolic activation in either of the two experiments.

Cashew nutshell liquid was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Human lymphocytes were exposed to cashew nutshell liquid in the presence and absence of metabolic activation in three experiments. The concentration ranges were 3 – 25 µg/mL, 0.78 – 37.5 µg/mL and 3.125 – 25 µg/mL in the first, second and third experiments. Harvest time for the cells was 20 hours for experiments 1 and 2, and 44 hours for experiment 3. Two replicates were conducted for each experiment. Positive and solvent controls were tested which responded appropriately. The cytotoxic concentrations were 12.5 µg/mL with metabolic activation and > 25 µg/mL without metabolic activation. The test substance did not induce a significant increase in the frequency of cells with chromosome aberrations or polyploid cells in either the presence or absence of metabolic activation.

Cashew nutshell liquid did not induce chromosomal aberrations in this assay.

Additional Information

Skin Sensitization

In a guinea pig maximization assay with Dunkin Hartley guinea pigs (20 females/dose), intra-dermal induction was conducted using 1% (w/v) in liquid paraffin and 1% (w/v) in a mixture of Freund's Complete Adjuvant plus distilled water. Topical induction was conducted using 25% (v/v) in liquid paraffin. Topical challenge was conducted with 5% or 2% (v/v) in liquid paraffin. Following intra-dermal induction, well defined, moderate to severe erythema was seen at 24- and 48-hour observations periods. Skin reactions observed at 24 and 48 hours after 5% topical challenge dose included very slight to well-defined erythema and very slight edema and desquamation. Very slight erythema in one animal and desquamation in three animals was present at 72 hours at the 2% challenge dose. All animals

showed an expected gain in body weight over the study period and no signs of ill-health were observed. The test substance produced a 70% (14/20) sensitization rate in the study and is considered a strong sensitizer.

Cashew nutshell liquid was sensitizing in this assay

Estrogenic Activity

An assay for estrogenic activity was conducted in *Saccharomyces cerevisiae* yeast modified to contain the human estrogen receptor (hER) and the reporter gene *lac-Z*. The concentrations tested were 0.049, 0.098, 0.20, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50 or 100 mg/L. Two replicates per concentration were tested. Positive controls were included and responded appropriately. No estrogenic activity was observed at any concentration tested.

Cashew nutshell liquid was not estrogenic in this assay.

Conclusion: Acute oral toxicity of cashew nutshell liquid in rats is low. Cashew nutshell liquid is a strong dermal sensitizer. Following repeated oral exposure of rats to cashew nutshell liquid in a combined repeated-dose/reproductive/developmental screening test, the target organs for toxicity were the liver, lungs, stomach and mesenteric lymph node. Slightly reduced body weight, increased salivation, hematological and clinical biochemistry effects were also noted. Females had increased relative liver weights. Statistical significance was not stated in the submission. Histopathological changes in the organs at the high-dose included higher incidence of alveolar macrophages in the lungs in females, sinus histiocytosis and/or foamy histiocytes in the mesenteric lymph nodes, hyperkeratosis and acanthosis of the forestomach in both sexes and duodenum-mucosal hypertrophy in males. No effects on reproductive or developmental parameters were noted in the study. Cashew nutshell liquid did not induce gene mutations and chromosomal aberrations.

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4. Hazard Characterization

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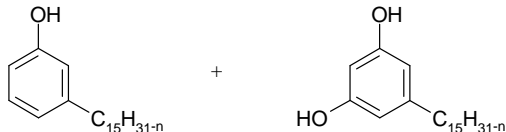
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The potential health hazard of cashew nutshell liquid is low.

5. Data Gaps

No data gaps were identified under the HPV Challenge Program.

APPENDIX

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	SPONSORED CHEMICAL Cashew Nutshell Liquid (CAS No. 8007-24-7)
Structure	<div style="text-align: center;">  </div> <div style="display: flex; justify-content: space-around; margin-top: 10px;"> <div style="text-align: center;"> <p>Cardanol 78 %</p> </div> <div style="text-align: center;"> <p>Cardol 8 %</p> </div> </div> <p style="text-align: center; margin-top: 10px;">+ 2% polymer + ~2% unidentified (where n = 0,2,4, or 6)</p>
Summary of Physical-Chemical Properties and Environmental Fate Data	
Melting Point (°C)	Not determined; this substance is a liquid under ambient conditions.
Boiling Point (°C)	Not determined; polymerization and decomposition occur before boiling.
Vapor Pressure (hPa at 25°C)	5.00×10^{-7}
Log K_{ow}	> 6.2
Water Solubility (mg/L at 25°C)	0.305 (20°C)
Direct Photodegradation	—
Indirect (OH [•]) Photodegradation Half-life ($t_{1/2}$)	0.4 – 1.3 h
Stability in Water (Hydrolysis) ($t_{1/2}$)	Not susceptible to hydrolysis
Fugacity (Level III Model)	<div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div style="text-align: right;">Air (%)</div> <div style="text-align: center;"><1</div> </div> <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <div style="text-align: right;">Water (%)</div> <div style="text-align: center;">1.9 – 3.8</div> </div> <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <div style="text-align: right;">Soil (%)</div> <div style="text-align: center;">28 – 30.9</div> </div> <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <div style="text-align: right;">Sediment (%)</div> <div style="text-align: center;">67.2 – 69.9</div> </div>
Biodegradation at 28 days (%)	96 Readily biodegradable

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	SPONSORED CHEMICAL Cashew Nutshell Liquid (CAS No. 8007-24-7)
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish 96-h LC ₅₀ (mg/L)	0.002 – 0.005 (Cardanol, estimated) 0.005– 0.011 (Cardol, estimated)
Aquatic Invertebrates 48-h EC ₅₀ (mg/L)	0.024 – 0.040 (Cardanol, estimated) 0.039 – 0.066 (Cardol, estimated)
Aquatic Plants 72-h EC ₅₀ (mg/L) (growth)	0.00011 – 0.00034 (Cardanol, estimated) 0.00031 – 0.00096 (Cardol, estimated)
Summary of Human Health Data	
Acute Oral Toxicity LD ₅₀ (mg/kg-bw)	> 1000
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	NOAEL = 150 (49-d) LOAEL = 1000 (49-d)
Reproductive Toxicity NOAEL/LOAEL (mg/kg-bw/day) Systemic toxicity Reproductive toxicity	NOAEL = 150 LOAEL = 1000 NOAEL = 1000 LOAEL > 1000
Developmental Toxicity NOAEL/LOAEL (mg/kg-bw/day) Maternal toxicity Developmental toxicity	NOAEL = 150 LOAEL = 1000 NOAEL = 1000 LOAEL > 1000
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	Negative
Other Information Sensitization	Strong Sensitizer

— indicates that endpoint was not addressed for this chemical.